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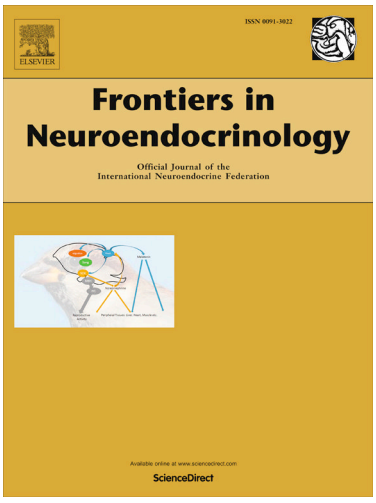

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An Energetic View of Stress: Focus on Mitochondria

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Abstract

Energy is required to sustain life and enable stress adaptation. At the cellular level, energy is largely derived from mitochondria – unique multifunctional organelles with their own genome. Four main elements connect mitochondria to stress: 1) Energy is required at the molecular, (epi)genetic, cellular, organ, and systemic levels to sustain components of stress responses; 2) Glucocorticoids and other steroid hormones are produced and metabolized by mitochondria; 3) Reciprocally, mitochondria functionally respond to neuroendocrine and metabolic stress mediators; and 4) Experimentally manipulating mitochondrial functions alters physiological and behavioral responses to psychological stress. Thus, mitochondria are endocrine organelles that provide both the energy and signals that enable and direct stress adaptation. Neural networks regulating social behavior – as well as psychopathological processes – are also influenced by mitochondrial energetics. An integrative view of stress as an energy-driven process opens new opportunities to study mechanisms of adaptation and regulation across the lifespan.

Keywords: mitochondrion; brain; ATP; mitochondrial signaling; mitokine; mtDNA; chronic stress; CORT; HPA axis; stress pathophysiology

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"*Without the vital force the material organism is unable to feel, or act, or maintain itself […]. Without the vital force the body dies.*" -- Samuel Hahnemann (1833)

1- Introduction

Life emerges when biological structures are animated by energy. Energy is defined as a fundamental entity of nature that is transferred between parts of a system in the production of physical change within the system, and usually regarded as the capacity for doing work [1]. Without energy, there is no life – molecules alone do not interact in meaningful ways, and complex structures do not assemble nor replicate. A crucial factor that distinguishes the breathing-living organism from the inanimate body (i.e., cadaver) is the flow of energy. There are no intrinsic differences in the molecular composition of dead and living organisms. But it is a required quality of living organisms to experience a constant flow of energy through and between its different parts. This flow of energy sustains the movement, chemical reactions, and dynamic changes in the position and organization of molecules that is required to think, feel, move, and execute every element of the stress response. Without energy, stress adaptation is not possible, and the body dies.

This review discusses the concept of stress as an energy-dependent coordinated process, with an emphasis on the key role that mitochondria plays in these processes. With a broad view of energy, we take a multi-level approach exploring the role of mitochondria in glucocorticoid and catecholamine metabolism, and the effects of stress hormones on energy substrate distribution within the body. We also consider the reciprocal action of steroid hormones on mitochondria. The influence of stress on food/energy-seeking behavior and emerging evidence regarding the influence of mitochondrial functions on mental health, social behaviors, and physiological stress reactivity are also discussed. An energetic view of stress

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adaptation and pathophysiology opens new possibilities to rationalize the integrated adaptive and maladaptive effects of stress on the brain and body.

2- Mitochondria transform energy

In human/mammalian cells, a substantial fraction of energy flow occurs through a specific endosymbiotic organelle, the mitochondrion. Mitochondria are the only organelles that contain their own genome – the mitochondrial DNA (mtDNA). The mtDNA encodes proteins essential to electron flow through a series of protein complexes called the respiratory chain (also known as electron transport chain, or ETC) [2]. As its name implies, the respiratory chain consumes oxygen. Mitochondrial respiration channels high-energy molecular intermediates through a series of enzymatic reactions, transferring chemical energy from food substrates and oxygen into a trans-membrane electrochemical potential ($\Delta\Psi m$) [3]. This stored energy is then used to power various mitochondrial functions, including adenosine triphosphate (ATP) synthesis, calcium uptake, protein and molecular import, biosynthesis of macromolecules and hormones, among others. Although mitochondria perform several “non-energetic” functions [4; 5], this article focuses on their role in energy metabolism. Thus, the breath provides oxygen to the mitochondria, sustaining membrane potential to ensure energy flow through the cell and the whole organism. Mitochondrial energy production then powers growth, healing, as well as the complex processes required for adaptation to the changing environment.

In cases where there are defects in the energy flow, life is disrupted and shortened by disease. For example, individuals with genetic mitochondrial disorders due to inherited mtDNA mutations, which impair respiratory chain function, suffer from debilitating and often lethal symptoms [6]. Organisms with severe mitochondrial dysfunction are incapable to sustain life and to adapt to dietary and physiological perturbations.

Stress – defined as a brain and body response aimed at promoting adaptation on the face of real or imagined threats to the organism’s homeostasis – cannot occur without energy.

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As discussed below, every aspect of the stress response requires energy: energy-dependent enzymatic reactions, transcription and translation required for gene expression and protein synthesis, neurotransmitter release and reuptake, hormone biosynthesis, sympathetic activation, behavioral adaptations, and long-term structural remodeling of organs and tissues are all “powered”, and to some extent regulated, by cellular energy levels. Even though, in fact, basic life-sustaining biological functions also require energy for their maintenance, the energy requirement for stress responses is above the basal needs of the organisms; hence, the emphasis here on the link between stress and energy demand.

3- Defining stress, allostasis, and allostatic load/overload

“Stress” is a term often used loosely given the difficulties experienced by scientists from the stress field to arise a consensus on its definition. Some authors have proposed to restrict the use of the term to conditions in which environmental demands exceed the natural regulatory capacity of an organism, particularly when the stressor is unpredictable and uncontrollable [7]. Other authors – particularly those concerned with the impact of stress on human mental and physical health – make a distinction between positive and negative (‘toxic’) stress conditions [8; 9]. Here, and from a practical point of view, we propose to distinguish between good, tolerable, and toxic stress.

“Good stress” arises from taking a chance on doing something one wants, like interviewing for a job, or giving a talk before strangers, and feeling rewarded when one is successful. There, stress mediators like cortisol and adrenalin promote adaptation during the challenge because they are turned on when needed and turned off when the challenge is over. “Tolerable stress” means that something bad happens, like losing a job, the end of a relationship, or the death of a loved one, but where the individual has the personal resources and support systems to “weather the storm” an be resilient. There, stress mediators are turned on and may stay turned on or are repeatedly turned on and off to promote adaptation; yet, by

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being chronically or repeatedly active, they may also promote potentially pathophysiological processes leading to cardiovascular, immune and metabolic dysregulation and changes in brain circuits involved in emotional regulation [10]. However, the individual's internal resources and external support systems minimize this aspect and eventually create a resolution that limits the long-term pathophysiological consequences.

"Toxic stress" means that something bad happens, like those events in "tolerable stress", but where the individual lacks internal resources or external support systems, and, as a result, there is a lack of sense of control that leads to a chronic physiological dysregulation that promotes pathophysiology and results in something called "allostatic load" and "overload", described below. Lack of control has been one of the defining features of psychological stress that leads to disease [11]. As a result, when toxic stress situations are prolonged, mental and physical health disorders develop over time. In this review, we use "stress" as an overall term for the body's need to adapt to life experiences, particularly those that fall into the categories of "tolerable" and "toxic" stressors that differ in duration, severity and degree of perceived control and which lead to some degree of allostatic load or overload.

The concept of "allostatic load" focuses on the paradox that the same mediators that help the body and brain adapt can also cause pathophysiology when overused and dysregulated. This terminology is more inclusive of life events than "stress". "Homeostasis" represents the physiological state which the body maintains to keep us alive – that is, body temperature, pH, and blood oxygen levels are kept within a narrow physiological range. In order to maintain homeostasis, our body triggers hormone secretion and activates the autonomic and central nervous systems (we call these "mediators" like cortisol, adrenalin, the immune system, and metabolism) to help us adapt. For example, these systems are activated when we get out of bed in the morning, walk up a flight of stairs, have a conversation. These systems are also activated to varying degrees when we are surprised by something unexpected, or get into an argument, or run to catch a train. We may colloquially refer to some of these experiences as

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"stressful", but for other experiences we do not, reflecting the imprecision of the term. Likewise, in research, "stress" is often used to denote molecular damage or dysfunction that occurs from a challenge, overuse, or even from toxins. But in a precise sense, any ever so slight perturbation to the system (such as standing up) induces a myriad of biological changes that aim to preserve homeostasis. So using the word "stress" does not really describe all of the underlying biology.

Rather, the term *allostasis* refers to the active process by which the "mediators" of the neuroendocrine, autonomic, metabolic, and immune systems help us adapt, as long as they are turned on in a balanced way when we need them and then turned off again when the challenge is over [12]. When that does not happen, these same mediators can cause unhealthy changes in brain and body. This is also the case when the *mediators* are not produced in an orchestrated and balanced manner – for example, too much or too little cortisol or an elevated or too low blood pressure. When dysregulation of these systems continues over weeks and months, we call it *allostatic load*, which refers to the wear and tear on the body that results from the chronic overuse and imbalance of the "mediators" [10; 13]. Allostatic load also includes the consequences of the health-damaging behaviors that often accompany a stressful lifestyle or are present in society, like and unhealthy diet, alcohol, smoking, inadequate sleep, lack of exercise, social isolation. Accumulation of belly fat is an example of allostatic load, as is the development of chronic hypertension.

When the wear and tear is strongest, we call it *allostatic overload* and this is what is occurring in toxic stress and accompanying health-damaging behaviors and what, hopefully, can be minimized in tolerable stress [14]. An example is when hypertension leads to coronary artery blockade, and the belly fat which contributes pro-inflammatory cytokines that accelerate the coronary artery blockade and cause insulin resistance in Type 2 diabetes [15]. Note, however, that we are talking, not about one mediator, like cortisol, but a host of mediators that are all released in allostasis in a coordinated, and in an energy-dependent manner, to help us adapt but which can also cause damage when overused and dysregulated. Below we consider the

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role of energy and mitochondria in the molecular, cellular, and organismal processes that orchestrate allostasis.

4- Energy is required for life and stress adaptation

Two billion years ago, life on earth was limited to unicellular life forms. Complex life arose from a symbiotic relationship whereby the ancestral eukaryotic cell engulfed an aerobic (i.e., capable of using oxygen to produce energy) bacterium [16]. This union of cell and bacterium, which eventually evolved into mitochondria populating the cell cytoplasm, likely constituted the igniting point for the evolution of complex life [17]. The larger amount of energy afforded by hundreds of oxygen-consuming mitochondria thus enabled the regulation of the human genome comprising of >20,000 genes, eventually culminating in the development of different cell types, multi-cellular tissues, organs, and breathing bodies [18]. Every cell of the human body contains a variable content of 100-1,000's of mitochondria, determined by energy demand of each cell type. Thus, the structure and function of the human body is closely linked to energy metabolism in general, and to mitochondrial function in particular.

Stress adaptation, or allostasis, also requires energy. Biologically, energy is necessary to allow plasticity both during development and to enable adaptation and remodeling of mature tissues and organs. The requirement for energy to enable change is a conserved principle well beyond biology. As a simple analogy, imagine a blacksmith attempting to alter the shape of a metallic object. The blacksmith must infuse considerable energy, in the form of heat, into the piece of metal only to make it responsive to the force of the hammer. Here, two different forms of energy are at play: one that contains little information but makes the structure malleable or plastic (i.e., the heat), and one more directed form that informs the transformation (i.e., the velocity and direction of the hammer). In stress biology, both mitochondrial oxidative phosphorylation and glycolysis contribute the "heat" that makes the organism malleable, providing the basic energy supply necessary to *enable* adaptation, or plasticity; whereas

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circulating neuroendocrine hormones and other factors interact with cellular-level epigenetic and molecular factors to *direct* adaptation.

In the presence of "heat" energy, circulating neuroendocrine factors both initiate and guide adaptation. For example, acutely glucocorticoids and catecholamines interact with their respective receptors to trigger processes that engage cellular plasticity mechanisms within neurons and specific brain regions [19]. Other circulating factors such as sex hormones, inflammation, and metabolic state may in turn influence the rate and extent to which stress mediators induce plasticity [19]. These factors, which modify the susceptibility of the brain and other systems to given stressors, manifest physiologically as vulnerability or resilience factors. On the other hand, systemic signals must interact with molecular and cellular factors contained within cells including age, genes, the epigenome, and other molecular mechanisms responsible for registering information from past experiences. Together, the information carried by circulating and cellular factors must be integrated, in an energy-dependent process, to direct coordinated cellular and physiological responses aimed at promoting adaptation in the face of stress (**Figure 1**).

4.1 The role of mitochondria in the epigenetic embedding of information

In order for the system to adapt, stress signals from the environment must be transduced into both short- and long-term biological changes in cellular composition and functions. A fundamental process at the origin of widespread cellular adaptations is transcriptional regulation of genomic elements, or changes in gene expression. This involving either the activation or repression of specific genes, or group of genes. Genes encode proteins, the basic building blocks that determine and maintain cellular specificity and function. But in complex multicellular organisms, function must be matched to the available supply of energy – a cell should only attempt to differentiate and divide if there are sufficient levels of the right energy substrates. Given the role of mitochondria in evolution of complex life forms, it is logical that a

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cell's gene expression, and in particular basic cellular operations such as cell division, growth and size regulation [20], and even cell death would be coupled to mitochondrial metabolic signals [5; 21; 22].

To achieve coupling of energetic environment and cellular behavior, information about the cellular environment are transformed, through signal transduction mechanisms, into metabolic intermediates (Acetyl CoA, α-ktoglutarate, succinate, NAD+) and reactive oxygen species that reach the nucleus [23]. Once in the nucleus, mitochondrial metabolic intermediates interact with the genome and the chromatin – the genes and associated regulatory proteins. There, metabolic signals contribute to activate or repress gene expression in two main ways.

First, they influence the interaction of transcription factors and co-activators with specific genetic elements, which influence transcript (messenger RNA, mRNA) formation [24]. For example, during hypoxia, mitochondria relocate near the nucleus where they produce an oxidized environment via reactive oxygen species (ROS) production, and which contributes to the activation of hypoxia-inducible factor 1 α (HIF1α) [25]. Energy deficiency also activates specific cytoplasmic energy sensors (mTORC1, AMPK) and their downstream transcriptional coactivators (e.g., PGC-1α) and transcription factors (e.g., PPARγ) that have widespread effects on gene expression.

The second and longer-lasting mechanism to transduce metabolic signals into transcriptional changes involves epigenetic (from the greek "epi", meaning "on top of") modifications of the chromatin. Combinations of epigenetic modifications of the DNA itself and on the histone tails, including but not limited to acetylation, methylation, phosphorylation, succinylation, ubiquitination, and other, form the basis of the epigenetic "code" [26; 27]. Chemical modifications of histone tails at specific loci on the genome can either repress or facilitate the expression of the associated genes, depending on their nature, location, and combination.

Interestingly, metabolic intermediates that are the substrates or co-factors for epigenetic modifications are all derived from the Krebs cycle and other metabolic pathways within

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mitochondria (reviewed in [28; 29]). For example, citrate, which is produced by the mitochondrial enzyme citrate synthase, is exported from mitochondria to the cytoplasm. There, citrate is transformed into Acetyl-CoA by ATP citrate lyase, which serves as a substrate for histone acetylation [30]. Normal mitochondrial metabolism is required for histone acetylation, as well as HIF-1α function and cell proliferation [31]. On the other hand, the removal of epigenetic marks also requires mitochondrial substrates. Histone and DNA demethylation reactions can only proceed in the presence of the cofactor α-ketoglutarate [32], also a metabolic intermediate of the Krebs cycle.

Thus, both the addition and removal of epigenetic marks are metabolically – or mitochondrially – regulated. Moreover, in addition to the shared chemical "language" between mitochondria and the epigenome, mitochondria are in close physical proximity to the nucleus and nuclear pores where molecular information transit in and out of the nucleus [22]. This presumably facilitates the diffusion of metabolic signals that reflect the integrated state of mitochondrial metabolism to the epigenetic machinery. Combined, these metabolic-to-epigenetic transduction systems may explain how, in an *in vitro* system, mitochondria regulate the expression of over half of the genes in the human genome [20]. Likewise, these systems provide a basis to explain how in complex organisms the epigenetic embedding of stress exposure may be regulated by mitochondrial metabolism.

5- Stress increases energy demand

Energy is present in two main forms in living organisms: i) as heat, which permeates all structures of living organisms; and ii) as chemical energy, in the form of chemical intermediates such as ATP that fuels specific enzymatic or biophysical reactions. Heat is the energy associated with the random motions of molecules. The origin of heat in the human body is the free energy released during the chemical breakdown of molecules. In mammals, a substantial amount of such reactions occurs in the mitochondrial matrix, a compartment filled with enzymes

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and insulated by a double-membrane layer. As a result, mitochondria is a site of cellular thermogenesis [33]. In mammalian cells, where enzymatic activity of the electron transport chain complexes is maximal, mitochondria are estimated to effectively function at temperatures around 50^{o}C [34].

Mitochondria are cellular sources of heat and account in part for the warm bloodedness of mammalian cells and organisms. In fact, the main mechanism of heat production and thermoregulation in infants, as well as in rodents, consist in uncoupling chemical reactions in the mitochondrial matrix from ATP synthesis (i.e., mitochondrial uncoupling) – chemical heat-releasing reactions occur unobstructed and thus increase core body temperature [35]. Chemically uncoupling mitochondria *in vitro* also results in increased cellular temperature [36]. Although a minor leak or uncoupling is ubiquitous in all mitochondria, physiological mitochondrial uncoupling occurs mostly in a specialized tissue – brown fat – through the action of uncoupling protein 1 (UCP1), which inserts into and makes the inner mitochondrial membrane leaky to protons, thus dissipating $\Delta\Psi m$ [37].

When the inner mitochondrial membrane is intact, the transmembrane gradient generated can be efficiently used to power the ATP synthesis with minimal heat release. In humans, only ~25% of the consumed oxygen is transduced into mechanical work during walking for example [38], indicating that this process is not completely efficient. This is evidenced by the rise in body heat during exercise. As for the ATP synthesized within mitochondria, it is then exported into the cytoplasm. In the cytoplasm, mitochondria-derived ATP provides the activation of energy for a large number of enzymes and chemical reactions that sustain cellular life and enable allostasis, including gene expression and protein synthesis.

During gene expression in the cell nucleus, the RNA polymerase (RNA Pol II) initiates and sustains transcription in an ATP-dependent manner [39; 40]. Subsequently, the synthesis of polypeptides by ribosomes also requires four ATP/GTP molecules for each amino acid incorporated into the nascent proteins [41], making protein synthesis a highly energy-

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demanding process [42]. Furthermore, these and many other reactions essential to life occur within the cytoplasm, whose chemical and electrical properties must be kept distinct from those of the extracellular environment. This is accomplished through the action of the 'energivorous' Na+/K+ ATPase pumps [43]. ATP hydrolysis by these reactions is also a substantial source of heat thought to contribute to thermogenesis [44]. Thus, maintaining the basic conditions for cellular life, from protein synthesis to the electrochemical cellular membrane potential, depends on the constant transformation of energy and heat release.

Beyond the cell, allostasis also involves widespread energy-demanding physiological changes. Consider for example the increase in heart rate associated with the stress response. The heart is a collection of different cell types where each contraction involves the hydrolysis of billions of ATP molecules, which are required to unidirectionally transmit the wave of depolarization/repolarization, for the actin-myosin cross-bridging that provide the power stroke of contraction during systole, and for Ca^{2+} pumping enabling relaxation during diastole [45]. Psychological stress alone increases heart rate and blood pressure by 10-20% [46], which would correspond to an equivalent increase in cardiac energy demand. In turn, this increase in cellular energy demand also results in systemic changes such as increased breathing rate and minute ventilation. These systems-level physiological changes ultimately reflect – or are subservient, to some extent – the increase in ATP-consuming reactions within the cell, and the corresponding increase in oxygen consumption within the mitochondria of the contracting heart. The same is also true of other metabolically active organs such as the brain.

Similarly, complex stimuli such as social interactions and other stressors are associated with behavioral responses that incur elevation in energy demand, also met by mitochondrial energy transformation. Locomotion, fighting, vocalization, licking and grooming, and any associated cognitive processes necessarily incur increased energy consumption at the cellular level [47]. Stress in particular increases cerebral energy demand including oxidation of glucose and oxygen consumption [48], reflecting increased mitochondrial activity within the brain.

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Interestingly, the stress-induced increase in cerebral energy demand may require adrenergic signaling by catecholamines [48; 49], indicating the interaction of stress mediators and mitochondrial metabolism (see *Section 9*).

Overall, biological process from the basic sustenance of vital function, acutely responding to life-threatening stressors, to the permanent adaptation to chronic stress, require substantial amount of energy. In humans and other mammals, the energetic demand of allostasis is largely met by mitochondrial respiration. Mitochondria transform circulating energy substrates into ATP and metabolic signals that endow biological structures with the necessary heat for plasticity, and interact with the information stored and communicated across organ systems to direct integrated, adaptive stress responses. This is in part achieved by the production of broad acting hormones like glucocorticoids and catecholamines.

6- Mitochondria synthesize and metabolize glucocorticoids and catecholamines

To match increases in mitochondrial energy demand, physiological mechanisms must be activated to ensure the availability of sufficient energy substrates systemically. This occurs via the action of hormones that increase circulating concentrations of glucose and lipids. Before we describe the effects of hormones on circulating levels of metabolic substrates and mitochondrial functions, we consider the role of mitochondria in the synthesis of these hormones and in their metabolism.

Mitochondria, which have so far been described as the major source of cellular energy, are also the site of synthesis for all steroid hormones [50]. This includes progestogens (e.g., progesterone), mineralocorticoids (e.g., aldosterone), glucocorticoids (e.g., cortisol and corticosterone), androgens (e.g., testosterone), and estrogens (e.g., estriol) (reviewed in [51]).

Glucocorticoids synthesis takes place in the zona fasciculata of the adrenal cortex, and occurs via a series of molecular reactions catalyzed within the mitochondria (**Figure 2**). The first

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step in steroidogenesis is the import of cholesterol through the mitochondrial membranes by the steroidogenic acute regulatory protein StAR [52]. StAR is activated by a protein kinase A (PKA)-dependent phosphorylation event induced by ACTH signaling, and is a rate-limiting step in steroid synthesis [50]. Once in the mitochondrial matrix, then the first enzymatic reaction transforms cholesterol into pregnanolone, catalyzed by the cytochrome P450 side chain cleavage enzyme ($P450_{SCC}$). Pregnanolone is then exported to the endoplasmic reticulum (ER) where a series of enzymatic reactions convert it to deoxycorticosterone (mostly in rodents) or 11-deoxycortisol (mostly in humans). The ER is closely associated with mitochondria in a number of tissues, where inter-organelle contacts are important for the function of mitochondria [53; 54]. The terminal reaction, catalyzed by the mitochondrial enzyme 11β-hydroxylase (11βH) then generates cortisol (human) or corticosterone (rodent) in the mitochondrial matrix. How glucocorticoids are released from mitochondria is not well defined, but presumably driven by its concentration gradient from the mitochondrial matrix, the cytoplasm, and systemic circulation in blood, and facilitated by the hydrophobic nature allowing it to diffuse through lipid membranes.

Another important class of hormones released in response to certain stressors are catecholamines, particularly norepinephrine (NE) and epinephrine (E). Both are derived from the neurotransmitter dopamine, itself generated from the amino acid tyrosine. Interestingly, the biosynthetic enzymes involved in catecholamine degradation, the monoamine oxidases MAO-A and MAO-B are anchored to the outer mitochondrial membrane [55]. Some reports also suggest that TH may be tethered to the mitochondrial surface [56; 57], although this may be tissue specific and inducible under certain conditions; more work is needed to examine this potential functional association of mitochondria with catecholamine synthesis and degradation.

Clinically, in relation to glucocorticoids, it has also been shown that primary mitochondrial dysfunction due to mutations in genes encoding mitochondrial proteins, can cause steroidogenesis defects. For example, NNT (nicotinamide nucleotide transhydrogenase) is a mitochondrial protein located in the inner mitochondrial membrane where it uses the transmembrane potential to regenerate NADPH and the intra-mitochondrial antioxidant system

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and impact energy metabolism [58]. Mutations of its gene cause severe familial hypocortisolemia [59; 60]. In mice lacking NNT, corticosterone is also lower and its release during acute psychological stress blunted by > 50% [61], demonstrating that normal mitochondrial function is required for general steroidogenesis and stress-induced corticosterone release. It remains unclear why the organism has evolved in such a way to position the key steps of steroidogenesis, including glucocorticoids and sex hormones, inside mitochondria. One possibility is that the mitochondrial matrix offers the optimal biochemical environment – both ionic and redox state – for the side chain cleavage and hydroxylation reactions that transform cholesterol into glucocorticoids [62]. This would seem consistent with the deleterious effects of NNT deficiency-associated redox imbalance on corticosterone/cortisol synthesis in mice and humans. Another possibility is that since these hormones are major regulators of energy metabolism (see below), coupling their synthesis to the major site of energy transformation in the organism (i.e., mitochondria) might have created some physiologically advantageous conditions – enhanced coupling of energy metabolism to endocrine responses – thus maximizing adaptation, and as a result, selection of mitochondrial steroid synthesis during evolution.

7- Stress hormones mobilize energy substrates

Mitochondria fuel the stress response in two main ways. As described above, they use substrates (glucose, lipids, amino acids) and oxygen to provide energy intracellularly, via the transformation of energetic substrates and oxygen into ATP. In a related way, as described above, they also contribute to the synthesis of stress hormones, which mobilize these same energetic substrates into the circulation.

Glucocorticoids (*gluc*ose, adrenal *cort*ex, ster*oid*) were originally named based on their ability to increase blood glucose concentration. Adrenalectomized animals are incapable to synthesize CORT, as are individuals with adrenocortical deficiency (Addison's disease), and as

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a result suffer from persistent hypoglycemia [63]. In humans, glucocorticoids elevates circulating levels of glucose and lipids metabolites within minutes [64], indicating their widespread role in the regulation of metabolism.

Glucocorticoids increase circulating glucose levels by acting simultaneously on the liver, skeletal muscles, and adipose tissue (reviewed in [65]). In these target tissues, glucocorticoids signal via the action of the glucocorticoid receptor (GR). In the liver, GR activation has pleiotropic effects where it induces chromatin remodeling [66] and transcriptionally induces key genes that encode for rate-limiting enzymes for gluconeogenesis (i.e., the synthesis of glucose from other carbon sources) [65; 67]. This leads to net hepatic glucose synthesis and output into the blood. In mice, inactivation of GR specifically in hepatocytes is sufficient to cause hypoglycemia [68], demonstrating the major role of liver glucose output in glycemic control.

Outside the liver, in skeletal muscle, GR activation acts in two main ways. First, it prevents glucose entry into myocytes by preventing the translocation of insulin-sensitive glucose transporters GLUT4 [69]. Second, GC activity antagonizes several elements of insulin signaling and inhibits the uptake of pyruvate, a breakdown product of glucose oxidation, by mitochondria [65]. The mechanism underlying this effect involves the transcription of pyruvate dehydrogenase kinase isoform 4 (*Pdk4*) by GC [70]. Because skeletal muscles are normally a major glucose “sink”, GC-induced inhibition of skeletal muscle glucose uptake and its oxidation by skeletal muscle mitochondria cause a substantial accumulation of glucose in the blood. In adipocytes also, where fat is stored, glucocorticoids antagonize insulin signaling and inhibits GLUT4 translocation to the plasma membrane, preventing glucose uptake and thus, as for skeletal muscle, passively raising blood glucose [71]. Overall, glucocorticoids plays a number of roles on target tissues aimed at increasing circulating glucose levels. Although not discussed in details here, glucocorticoids regulate multiple processes related to lipid metabolism that culminate in increasing their systemic levels.

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In the absence of real stressors and without the need to engage in physically demanding behavioral responses, stress hormones can dysregulate metabolism. In humans, individuals with higher cortisol circulating levels under resting (non-stressed) conditions have higher levels of glucose and triglycerides, and a higher score reflecting insulin resistance and a pre-diabetic state [72] (**Figure 3A-B)**. Likewise, in mice, chronic glucocorticoid administration results in elevated triglycerides, glucose intolerance, and weight gain [73]. These metabolic changes are associated with higher levels of insulin and leptin hormones, indicating cross-talk between these systems. And in addition to their effects on metabolism, chronic glucocorticoid administration can also induce physical inactivity and depressive-like behavior [73; 74].

These coordinated physiological changes cooperate to increase circulating levels of energetic substrates to fuel the mitochondria of metabolically active organs, such as the brain and the heart, most in need during stress. In this emerging mito-metabolic picture, mitochondria-derived hormones from the adrenal cortex, a specialized tissue, calls upon energy stores and reprograms metabolism in other tissues. This represents a form of “mitocrine” signaling – systemic endocrine signaling by a mitochondria-derived hormone (**Figure 3C**). Mitochondria-derived molecules produced in certain cells thus affect the function of other cells and their mitochondria in a cell non-autonomous manner [75]. Therefore, glucocorticoid hormones synthesized in mitochondria can be regarded as mitokines.

Mitochondria also produce and secrete other mitokines, such as humanin, mitochondrial open reading frame of the 12S rRNA-c (MOTS-c), and small humanin-like peptides (SHLP1-6), which influence systemic energy homeostasis and regulation of whole organisms functions (reviewed in [76]). Together with their role as site of steroid hormone synthesis, these discoveries are positioning mitochondria as important endocrine organelles particularly active during stress.

8- Glucocorticoids: Not just “stress”

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Glucocorticoid secretion has another important function from responding to stressors, namely, coordinating waking and sleeping functions during the diurnal cycle. A defining characteristic differentiating wakefulness and sleep states is that the metabolic demand, along with body temperature, which decreases significantly (>15-30%) during sleep [77; 78]. Cortisol levels are lowest in the early phase of sleep, and undergo an elevation before wakening, promoting increased locomotor activity and appetite [79]. A flat glucocorticoid diurnal rhythm leads to a sluggish stress-induced increase of ACTH [80; 81]. Plasticity of the brain extends to the day-night (diurnal) cycle of waking and sleeping. Some, but not all, synapses in many parts of the cerebral cortex turn over during the diurnal cycle due to the ultradian fluctuation of glucocorticoids, and interfering with that cycle by elevated glucocorticoids at the wrong time of day interferes with motor learning, like learning to play golf [82]. Considering how many ways modern humans interfere with the natural day-night rhythm, for example, by turning on a light in the middle of the night, this is a lesson to all to give the “wisdom of the body” a better chance to help us. Another way we interfere with the natural cycle is through shift work and jet lag. An animal model of shift work caused dendrites in the prefrontal cortex to shrink and the animal to become cognitively rigid when challenged with a memory task that required changing the rules [83]. The prefrontal cortex governs “self-regulation” and the ability to regulate emotions and impulses as well as working memory.

Moreover, the shift work animals became fatter and insulin resistant, signs of pre-diabetes and depressive-like behavior [83]. Shift work in our own species is associated with greater obesity, diabetes, cardiovascular disease and mental health problems [84; 85]. This story is relevant to the health effects of shift work in transit workers [85]. One of the mediators for circadian disruption-related obesity, acting peripherally, are endocannabinoids acting via the type-1 cannabinoid receptor CB1 [86]. Disrupted patterns of glucocorticoids are linked to circadian disruption induced obesity, and CB1 activity is necessary for the obesogenic effects of glucocorticoids [86]. The CB1 receptor, which localize at the plasma membrane of the presynaptic terminal, is also found in mitochondria [87]. Upon activation, mitochondrial CB1 can

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decrease mitochondrial oxidative capacity and modulate memory in a mitochondria-dependent manner [88]. Thus, as discussed in the next section, glucocorticoids and other systemic signaling molecules may converge upon mitochondria to induce systemic changes in the metabolism of the brain and multiple other tissues.

9- Glucocorticoids influence mitochondrial functions

In an intriguing reciprocal connection, mitochondria are not only the source of glucocorticoids and other systemic signaling molecules, but are also affected by them. Here we specifically focus on the effects of glucocorticoids on mitochondria and the some of the underlying mechanisms. Mitochondria have emerged as major players in steroid hormone actions and containment of excitotoxicity because of their ability to generate free radicals and to sequester Ca^{2+} ions to contain that process, as well as to express genes from its own genome and receive nuclear coded genes that, together, regulate a host of important cell functions [4]. Mitochondria are also known to respond to GR translocated into them [89; 90]. In cultured neurons, the synthetic glucocorticoid dexamethasone exerts biphasic effects on mitochondrial function in which physiological levels of glucocorticoids promote Ca^{2+} sequestration, moderate oxidation and maintain mitochondrial membrane potential while supra-physiological glucocorticoid levels start to do so but fail after 24 h and lead to a failure of all three measures [91]. In other cell types, chronic glucocorticoid treatment can reduce the activity of specific mitochondrial electron transport chain complexes and increase mitochondrial ROS production [92; 93]. The underlying mechanisms for these effects are not fully understood, but there are three glucocorticoid response elements (GREs) on the circular mtDNA [90], where GR likely bind and influence mtDNA gene expression [94; 95].

It is also important not to ignore estradiol, and possibly other steroid hormones, which regulates mitochondrial respiratory capacity and oxidative stress, since estradiol receptor beta is also translocated into mitochondria and has neuroprotective actions [96]. In particular, after a

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surgical menopause, as shown in rhesus monkeys, cortical neurons contain circular mitochondria associated with oxidative stress [97; 98], where estradiol treatment may be particularly important as a neuroprotective strategy. The GR is ubiquitously expressed across tissues, and the mechanisms regulating how mitochondria in different cell types respond to glucocorticoid stimulation remains to be elucidated.

10- Effects of psychological stressors on food- and energy-seeking behaviors

Stress increases energy demand at the cellular level and activates systemic mitocrine and endocrine processes to sustain this increased demand. Based on the increased energetic needs associated with stress responses and allostasis, and the energy mobilizing effect of mitochondria-derived CORT, it is logical to expect that stress would be coupled to changes in food- and energy-seeking behaviors. Indeed, there is evidence, described below, that psychological stress triggers eating behavior, shifts macronutrient preferences to denser calories, and shift fat storage to the intraabdominal fat stores, a form of energy storage with more rapidly mobilized free fatty acids than fat depots elsewhere, such as in subcutaneous stores.

In animal studies, historically stressor exposure led to anhedonia, lack of interest in food, and weight loss. However, these conclusions were based on loss of interest in the standard lab chow. Once studies started making highly palatable food (high fat, high sugar) accessible, the opposite effect of stress on food consumption was observed. In rodent models, when animals are given intermittent access to calorically dense junk food, they tend to overeat and gain weight, likely due to changes to the reward system. However, if on top of this, they are also exposed to psychological stress, they develop excessive drive to eat, high cortisol, and binge eating [99]. When rats are exposed to stress, particularly subordination stress, and given the opportunity to consume lard or sugar, they binge eat [100] and develop excessive abdominal fat [101], a highly reliable source of energy for times of stress.

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In humans, there are also well documented relationships between exposure to both acute and chronic stress with greater food seeking and food intake, particularly of comfort food [102; 103]. A classic study also showed that when administered glucocorticoids men had increased energy expenditure but also a disproportionate increased appetite, resulting and weight gain [104]. In a double-blind, randomized, cross-over study assessing metabolic responses to a high fat meal in relation to stress, previous day stress was associated with lower fat oxidation as well as higher insulin production [105], both physiological processes that favor "energy storage". Together, these studies show that stress and glucocorticoids in particular may lead to energy seeking and replenishment behavior. This can help maintain allostatic balance both acutely and chronically by replenishing adipose energy stores over periods of stress exposure.

Although this has not been examined in clinical studies of feeding behavior, it may be that mitochondria, via their dynamic processes of fusion with each other and their interaction with other organelles, play a role in sensing circulating levels of energy substrates. Mitochondria can respond within minutes to levels of glucose and lipids by undergoing fusion (elongation and branching of smaller mitochondria [106; 107]) or fission (fragmentation of longer mitochondria [108; 109]) (reviewed in [110]). In turn, changes in mitochondrial shape or morphology are associated with functional recalibrations linked to mitochondrial signaling [111]. Based mostly on evidence from *in vitro* systems and animal models, chronic inhibition of mitochondrial fusion leading to persistent fragmentation of mitochondria might contribute to the adverse and pro-aging effects of metabolic stress [112]. In physiological conditions, changes in mitochondrial shape enable neurons of the hypothalamus to sense glucose [113] and lipid [114; 115], triggering satiety and regulating insulin and energy balance. Thus, dynamic mitochondrial responses to circulating energy levels may be involved in regulating allostasis systemically.

The evidence reviewed in this section suggest that stress and the associated mitochondrial-derived glucocorticoids play a critical role in furthering energy seeking behavior.

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Combined with evidence presented earlier, there are therefore three main ways by which mitochondria contribute to the metabolic aspect of stress responses: i) mitochondria provide energy in the form of ATP and metabolic signals to power cellular events during stress; ii) they produce stress hormones that coordinately ensure adequate circulating levels of energy substrates; and iii) mitochondria in specialized tissues sense and monitor circulating levels of metabolic substrates and generate signals that direct food seeking behavior. These levels are obviously nested within one another, where eating behavior supply food substrates for the circulation, which provides the fuel for mitochondria to convert into ATP. From an evolutionary perspective, stress-induced energy/food-seeking behaviors likely aim to replenish energy stores that are depleted during the active coping process.

Thus, mitochondria in different tissues execute different roles but collectively, via communication among each other, ensure the efficient sensing, integration, and signaling of metabolic information. This multi-site stress regulation of metabolism is reminiscent of distributed control networks, recognized to optimize the function of complex systems in complex environments [116]. This intriguing set of mitochondrial roles – from cellular to behavior – lead us to consider the potential involvement of these multifunctional organelles as a link between metabolic dysregulation and psychopathology.

11- Mitochondria link metabolic dysregulation and depression

Mitochondria play a key role in the allostasis of neurotransmission and depression. Dysfunctional mitochondria promote oxidative stress and the inflammatory tone that contribute to the depressive state [117]. A major determinant of mitochondrial function and of the signals they generate is the energy substrates they metabolize. Within the brain and other tissues, mitochondrial fatty acid metabolism is facilitated by esterification with carnitine [118]. A short-chain acylcarnitine, acetyl-L-carnitine (LAC), not only protects and enhances mitochondrial

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function [119] but also acts as an acetyl donor for metabolism and for epigenetic modification of histones [120] and for mitochondrial proteins in a biphasic manner [121; 122]. Under biphasic control by glucocorticoids, mitochondria sequester calcium released by NMDA receptor activation and glutamate release [123]. But glutamate also synergizes with glucocorticoids to promote shrinkage of dendrites and turnover of spine synapses [124]. The metabotrophic glutamate receptor mGlu2, which is regulated epigenetically via acetylation of lysine at position 27 on histone H3 (H3K27) [120], presynaptically contains and restricts spontaneous glutamate release; down-regulation of this receptor leads to spillover of glutamate that inhibits neurogenesis and promotes dendritic shrinkage and spine synapse loss [124; 125].

This condition, involving a depressive-like behavioral state, is associated with LAC deficiency. In animal models, depression can be rapidly ameliorated within 3-5 days by LAC supplementation, while classical antidepressants, if efficient at all, will show effects after several weeks. As an acetyl donor via acetyl-CoA [126] for H3K27acetylation, LAC epigenetically upregulates mGlu2 expression and reduces the glutamate overflow [120; 127]. LAC itself may promote mitochondria biogenesis and enhance mitochondrial oxidative capacity in the context of aging and depression [119]. In lower organisms like worms, mitochondrial dysfunction alone is sufficient to induce histone acetylation and methylation [128]. This suggests that mitochondrial remodeling, including calcium buffering and reducing ROS generation, and mitochondrial signaling reducing inflammatory tone as well as donating acetyl groups for histone acetylation, may collectively contribute to the antidepressant-like actions of LAC [117].

Moreover, LAC deficiency in animal models is associated with metabolic dysregulation, including insulin resistance, elevated triglycerides and leptin that, like the depressive-like behavior, is rapidly corrected by LAC treatment [129]. Connecting this to LAC and its actions, research shows that a ketogenic diet that relies on and activates mitochondrial oxidative metabolism ameliorates insulin resistance and Type 2 diabetes, and also increases LAC levels [130]. Furthermore, a ketogenic metabolite, beta-hydroxybutyrate, is an histone deacetylase inhibitor [131] that blocks removal of acetyl groups from lysine residues on histones and has the

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same rapid effects on mGlu2 as LAC. Taken together, mitochondrial dysregulation appears to play a key role in the progression from metabolic dysregulation to depression and dementia, and thus connects systemic dysregulation with central nervous system allostatic load [132].

12- Mitochondrial function in the brain influences social behaviors

A link between mitochondrial function and social behaviors has started to emerge in recent years. Notably, an increasing number of studies are reporting mitochondrial dysfunction in Autism Spectrum Disorder (ASD) [133; 134], a neurodevelopmental disorder involving core alterations in social behaviors. Key recent evidence includes reports indicating redox metabolism abnormalities in autistic children associated with mitochondrial disease [135] and genetic evidence for pathogenic mtDNA mutations as a potential cause for ASD [136]. Beyond autism, a recent study has identified an association between a mitochondrial DNA (mtDNA) single nucleotide polymorphism (SNP), which affects the regulation of mitochondrial calcium levels related to energy production, with aggression and leadership in children with ADHD [137].

While the reported clinical data provides correlational data, preclinical studies in rodents are starting to provide evidence that metabolic alterations contribute to social dysfunctions. For example, treatment with a ketogenic diet – a high-fat low-carbohydrate diet that enhances mitochondrial function – was able to ameliorate impaired mitochondrial respiration and deficits in social behaviors in a valproic acid model of autism in rats [138]. In another study, acute infusion in rodents of resveratrol, a compound that activates AMPK-induced mitochondrial biogenesis, counteracted diminished sociability induced by peripubertal stress [139]. Similarly, treatment with the antioxidant N-acetyl cysteine reversed impairment in social isolation and accumulated striatal ATP levels observed in a rat model of social isolation rearing stress in rats [140].

Further insights for a key role of mitochondrial function in specific brain regions in influencing complex social behaviors have been provided by a series of studies in rats relating anxiety with diminished social competitiveness [141; 142], a phenomenon that has also been

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highlighted in humans [143]. In rats, lower mitochondrial function in the nucleus accumbens was observed in high-anxious animals compared to their less anxious littermates, and was causally implicated in their low social competitiveness [141]. More specifically, high-anxious animals that are prone to become subordinate during a social encounter exhibited reduced mitochondrial respiratory capacity, decreased ATP levels, and increased ROS production in the nucleus accumbens. Furthermore, micro-infusing specific mitochondrial electron transport chain inhibitors into the nucleus accumbens reduced social rank, recapitulating the low probability to become dominant in anxious animals. Conversely, intra-accumbal infusion of nicotinamide, an amide form of vitamin B3 known to enhance brain energy metabolism, prevented the development of a subordinate status in anxious rats [141]. Additionally, treatment with a low dose of the anxiolytic diazepam was effective to facilitate social dominance, ameliorating both the competitive disadvantage and low mitochondrial function in the nucleus accumbens displayed by high-anxious rats [142].

Interestingly, homecage dominant and subordinate male inbred C57BL/6J mice were found to display differences in energy metabolites in the nucleus accumbens. Data from ^{1}H-NMR spectroscopy indicated that subordinates show lower levels of energy-related metabolites than dominant mice [144]. When exposed to chronic social defeat, dominant males were the ones that specifically showed vulnerability to display depression-like behaviors. While levels of brain energy metabolites increased in ‘resilient’, subordinate mice, metabolites in dominant, ‘vulnerable’ animals tended to be reduced following exposure to chronic social defeat [144].

While these studies strongly point out at a relevant role for mitochondria in organizing complex behaviors, future work should elucidate how mitochondrial function and energy metabolism contributes to neuronal and circuit properties that eventually regulate specific social behaviors and vulnerability/resilience to stress. One related synergistic process by which mitochondria may regulate stress vulnerability/resilience is by regulating the reactivity of neuroendocrine, immune, and metabolic axes to stressors.

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13- Mitochondria regulate physiological stress reactivity

During evolution, the ability to generate whole-body physiological response to environmental and physiological challenges was likely a critical driving force behind natural selection [145]. The integrated energy-demanding stress responses, which involve transcriptional regulation, the secretion of various stress hormones such as glucocorticoids and catecholamines, acute metabolic changes, inflammatory mediators, neural plasticity, and many others, determine an organisms' ability to thrive and adapt, or become ill in the face of stressful situations [146]. In the context of this review, and in an attempt to explain individual differences in vulnerability to stress is, a critical question is whether differences in mitochondrial energy metabolism influence how the organism responds to complex stressors.

The evidence reviewed above has described pathways and mechanisms whereby mitochondria directly contribute to gene expression regulation through direct and epigenetic mechanisms, the synthesis of important stress mediators, metabolic regulation, and neural circuits that orchestrate complex behaviors. To examine the role of mitochondria in the physiological stress response, we tested the hypothesis that abnormal mitochondrial functions would differentially modulate the organism's multisystemic response to a psychological stressor. In mice, it is possible to genetically modify different domains of mitochondrial function: mitochondrial respiratory chain function, energy exchange, or the intramitochondrial redox status. In a collaborative study, we found that mitochondrial dysfunctions altered hippocampal gene expression, the hypothalamic-pituitary-adrenal axis, sympathetic adrenal-medullary activation and catecholamine levels, the inflammatory cytokine IL-6, circulating glucose and lipids in response to stress (**Figure 4**) [61]. Each mitochondrial defect generated a distinct whole-body stress response signature. Thus mitochondria are stress-response modulators, with implications for understanding the mechanisms of stress pathophysiology and mitochondrial diseases [147]. In a 'non-linear' way reminiscent of the transcriptional reprogramming in the cells with mtDNA mutations [20; 148], this study found that each mitochondrial defect caused a

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unique multisystemic stress response signature sometimes opposite to each other, depending upon the nature of the mitochondrial defect [61].

Psychological or physical stress triggers neuroendocrine, inflammatory, metabolic, and transcriptional perturbations that ultimately predispose to disease via allostatic load/overload [149]. The systemic neuroendocrine consequences of mitochondrial defects have implications for our understanding of the pathogenic mechanism underlying mitochondrial disease onset and progression. Stress influences the biology of multiple diseases including cancer growth and metastasis [150; 151], diabetes [152], neurodegenerative disorders [153], as well as cellular aging [154] and age-related physical and cognitive decline [149]. Thus, combining the notions that mitochondria regulate the activation of stress responses and release of allostatic mediators, and that stress response mediators influence disease trajectory, an emerging possibility is that mitochondrial dysfunction – or mitochondrial allostatic load (MAL) – may contribute to translating stressful experiences into pathophysiological processes [155]. In humans, much research is still needed to ascertain to what extent mitochondria regulate physiological responses to both positive and negative psychological states, whether they partly underlie the drive for energy intake, and whether mitochondrial stress transduction contribute to stress pathophysiology and maladaptation.

14- Sexual dimorphism in mitochondria and stress physiology

It must be noted that the female and male organisms have qualitatively different mitochondria, but that little is known about the interaction with stress. Indeed, even if all mitochondria and the mtDNA are uniquely contributed by the mother [156], differences in protein composition and function are acquired during development and as a result, multiple facets of mitochondrial biology differ by sex in adult animals [157]. This is, in part, due to the fact that sex hormones regulate mitochondrial function and biogenesis [158]. Metabolomic signatures also, which indirectly reflect mitochondrial and cellular metabolism of the whole organism, show that

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up to one-third of metabolites differ between men and women [159]. In relation to stress, a recent meta-analysis of the literature on the effects of induced stress on mitochondrial structure and function revealed that *all* studies to date have been conducted in male rodents [160]. The studies of social behavior and stress regulation described in the above sections have also been conducted exclusively in male animals. In humans, the opposite trend is beginning to appear, with women being predominantly studied [160].

Two main factors might have contributed to this unbalanced state of the field: i) the need for larger and more complex study designs when including both sexes, and ii) the largely false belief that hormonal fluctuations in female animals introduces additional variability that weakens conclusions and is unnecessary to the progress of science. The former argument is valid, as studying both sexes with equal power necessarily doubles sample sizes and in some cases costs. However, the argument about female animals being more variable has been demonstrated not to be accurate in neuroscience and biomedical research outcomes [161]. In fact, inclusion of both sexes in basic research may even drive discovery [162], as well as the production of more directly translatable pre-clinical and clinical research. Therefore, based on known sex differences in mitochondrial biology, in stress physiology, and disease risk in humans, future studies would benefit from an equal inclusion of both sexes.

15- Conclusions section

Mitochondria were essential to the development of complex multicellular life forms, and only recently have we started to develop a scientific understanding of the interplay between specific aspects of mitochondrial function and stress responses. The mechanistic pre-clinical findings reviewed above provide converging evidence that mitochondrial energetics may directly impact neuroendocrine and metabolic responses to psychological stress, epigenetic regulation within the brain, food and energy seeking behaviors, psychological states such as depression, and complex social behaviors. It will be a fascinating challenge for behavioral neuroscientists to

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determine whether mitochondrial energy production capacity or other mitochondrial signals influence psychological states and social behaviors in humans also, and if so, whether interventions targeted at mitochondria can influence complex behaviors and promote adaptation and health.

Much attention in the past decades has been devoted to mapping the contribution of specific anatomical structures within and outside the brain to the stress response, including neuroendocrine mediators and the immune system. The brain has been regarded as a central organ of adaptation [163]. The work reviewed above implicates mitochondria as a central *organelle* of adaptation, operating at multiple levels within the stress response. Via their effects on neuroendocrine mechanisms, mitochondria drive adaptive signaling processes and behaviors. Simultaneously, mitochondria sense changes in energy demand and rapidly respond – in shape and function – to energy-mobilizing glucocorticoids and catecholamine hormones. It is enlightening to consider why evolution has routed the production of glucocorticoids and sex hormones within mitochondria of specialized steroid-secreting cells (adrenal cortex, gonads). In turn, mitochondria in other tissues like the brain, muscles, and liver sense and functionally respond to glucocorticoids via the action of GR and other “nuclear” receptors on the mtDNA. Mitochondria are both mediators and targets of the main stress axes. Therefore, glucocorticoids be regarded as a mitokines (i.e., mitochondria-derived hormones) mediating mitochondria-to-mitochondria communication among distant sites throughout the organism. Much remains to be discovered about the mechanisms and implications of mitocrine signaling.

Mitochondria play vital role in sustaining basic life processes and those that specifically become activated during allostasis. An “energetic” scientific perspective of stress and the downstream (mal)adaptive consequences invites a focus on the communication systems and mechanisms that ensure and direct the flow of energy towards adaptive processes. Energy and mitochondria are primary drivers of these processes. Moving away from a predominantly anatomically-directed scientific framework, we must consider a model of stress focused on understanding how information and energy in their different forms are exchanged between the

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environment, the organism, organelles, and the plastic epigenome. Mapping the mechanisms underlying these exchanges will likely open the door to next generation approaches to identify and target maladaptive responses early before they manifest as disease, and to foster physiological responses underlying successful adaptation and resilience.

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Figure legends

Figure 1

Mitochondria sustain life and enable stress adaptation. (**A**) Within mammalian cells, mitochondria perform exactly the opposite reaction as the plant chroloroplasts. Plants produce oxygen and food substrates (carbohydrates, lipids), which are used within mitochondria to power oxidative phosphorylation and ATP synthesis. In this process, mitochondria release carbon dioxide (CO_2) and water (H_2O), the substrates required by plants, thus sustaining the cycle of life. (**B**) Stressors interact with information contained within the organism, such as genetically encoded biological constitution, memories of past events, and the current psycho/physiological state reflected by molecular, neuroendocrine, immune, and metabolic factors. Together, this generates unique adaptive stress responses and behaviors. Without energy, stressors would have no effect on the organism. But in the presence of heat and chemical energy, stressors and information interact in meaningful ways to enable stress adaptation.

Figure 2

Cortisol and catecholamine metabolism. (**A**) Steroidogenesis takes place in mitochondria. The first step involves the rate-limiting import of cholesterol into mitochondria by the steroidogenic acute regulatory (StAR) protein, followed by the side chain cleavage to pregnenolone by $P450_{SCC}$, three enzymatic reactions in the endoplasmic reticulum, and the final 11-β-hydroxylase reaction catalyzing cortisol synthesis in the mitochondrial matrix. Mitochondria are particularly enriched in the adrenal cortex where glucocorticoids are synthesized in response to ACTH. Also shows is the catecholamine pathway, including tyrosine hydroxylase, which may become associate with mitochondrial membranes under some conditions (see text for discussion), and the mitochondria-anchored monoamine oxidases A and B, which degrade catecholamines in specific tissues. Degradation products are not shown. (**B**) Electron micrograph of the zona fasciculata of the hamster adrenal cortex with pseudocolored mitochondria (orange) and endoplasmic reticulum (purple). Picture modified from [164].

ER: Endoplasmic reticulum; StAR: Steroidogenic acute regulatory protein; $P450_{SCC}$: Cytochrome P450 side chain cleavage (Cyp11a1, inner mitochondrial membrane bound); 17aH: 17-alpha hydroxylase; 3βHSD: 3β-hydroxysteroid dehydrogenase; 21H: steroid 21-hydroxylase; 11βHSD: 11-β-hydroxylase; TH: Tyrosine hydroxylase ; AADC: Aromatic L-amino acid decarboxylase; DBH: Dopamine β-hydroxylase; PNMT: Phenylethanolamine N-methytransferase; MAO-A/B: Monoamine oxidase A/B.

Figure 3

Interplay of primary stress mediators, glucose and lipids, and mitochondria. (**A**) Fasting blood glucose levels and the homeostatic model assessment of insulin resistance (HOMA-IR) index reflecting insulin resistance, and (**B**) blood triglycerides as a function of resting plasma cortisol concentration categories. These data reflect dose-response association between glucocorticoids and metabolic stress, in line with the glucose-mobilizing properties of CORT.

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Data from a population sample of 286 individuals, adapted from [72]. (**C**) Mitocentric model of mitochondrial substrate mobilization to serve their bioenergetic needs in target tissues. Mitochondria in the adrenal cortex are the source of CORT, whereas mitochondria in other tissues are the recipient of resulting increases in circulating energy substrates used for oxidative phosphorylation, ATP synthesis, and metabolic signaling.

Figure 4

Mitochondrial defects cause unique stress reactivity patterns in mice. (**A**) Mice with normal mitochondria (wild type, WT) were compared with mice with mitochondrial defects, including four different genes involved in energy production (respiratory chain Complex I, ND6 subunit; respiratory chain Complex IV, MT-COI subunit), energy transfer (adenine nucleotide translator 1, ANT1), and mitochondrial oxidative stress (nicotinamine nucleotide transhydrogenase, NNT). All mice were exposed to 30 minutes of restraint stress with sequential tail blood collections. (**B**) HPA axis response kinetic indicated by corticosterone increase during stress, and recovery. (**C**) This acute stressor also caused hyperglycemia. This graph shows the juxtaposition of the stress-induced corticosterone (CORT) levels over the first 30 minutes and the associated increase in circulating blood glucose. Note that the mitochondrial defect causing excess corticosterone release simultaneously causes the lowest glucose increase, whereas the NNT defect that blunts corticosterone release causes the highest glucose response. These results indicate an uncoupling of neuroendocrine and metabolic allostasis. (**D**) Each genetic defect produced a unique stress response signature, here illustrated as a heatmap showing results of an unsupervised hierarchical clustering analysis of gene expression, neuroendocrine, inflammatory, and metabolic measurements (n = 77 parameters). (**E**) Principal component analysis illustrating qualitatively and quantitatively distinct whole-body stress response patterns for each mitochondrial defect. Figures adapted from [61].

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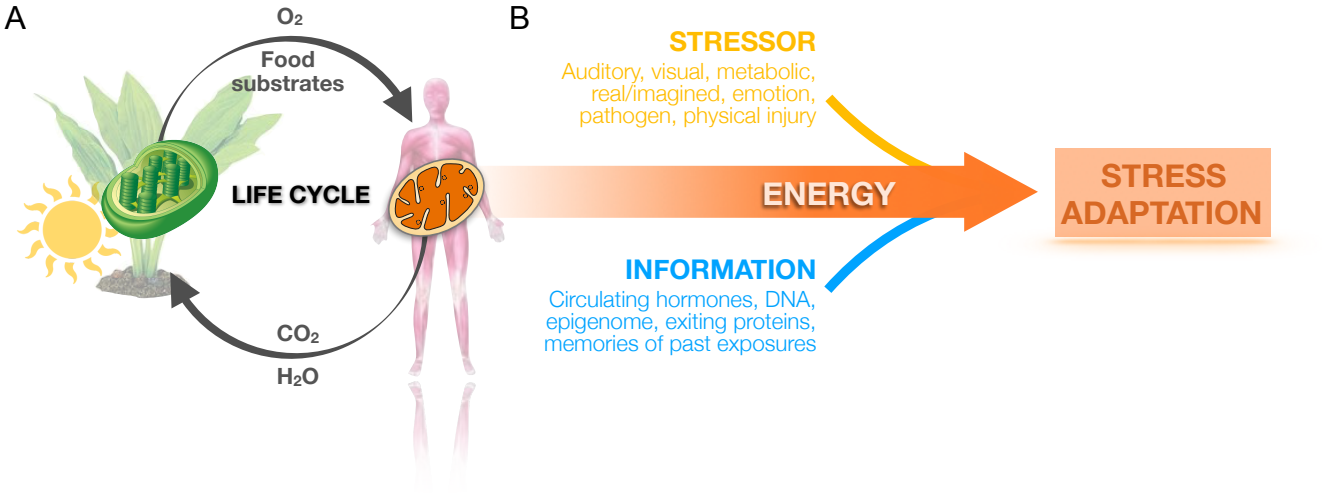

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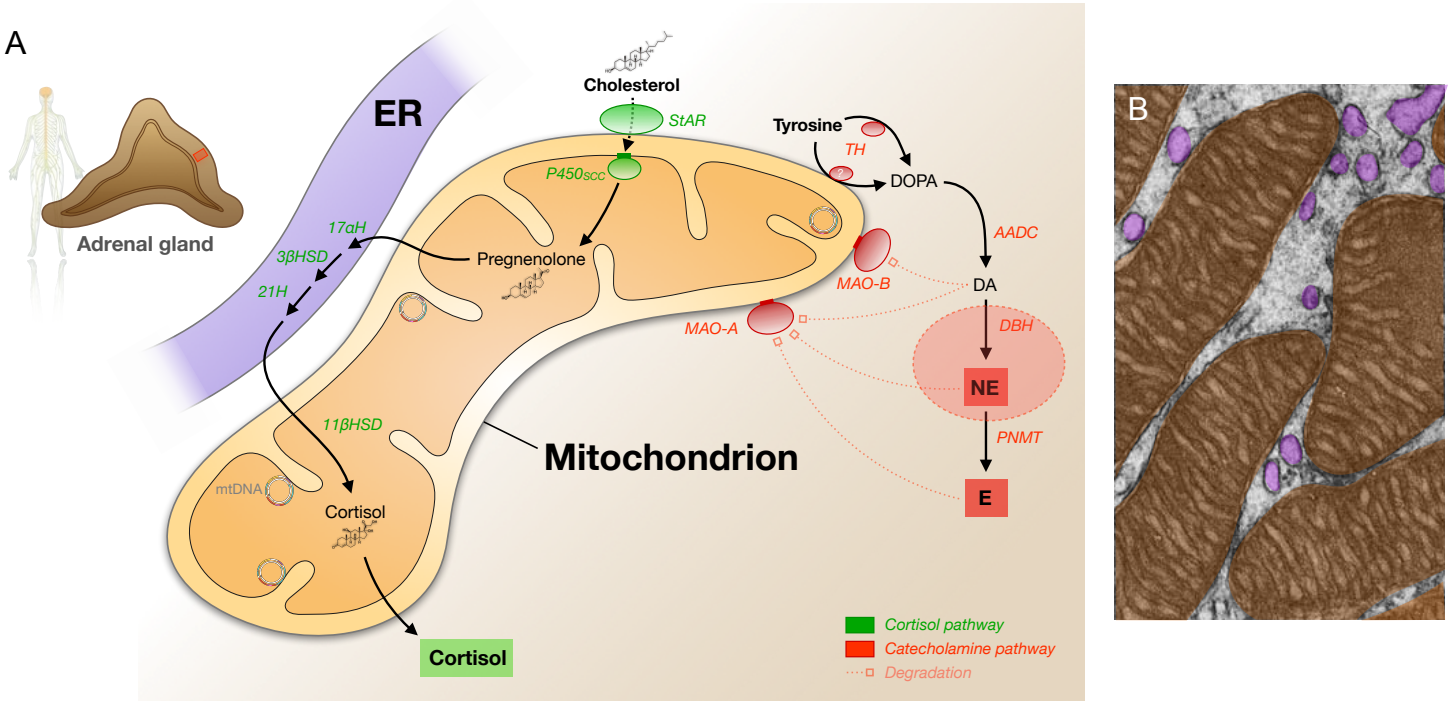

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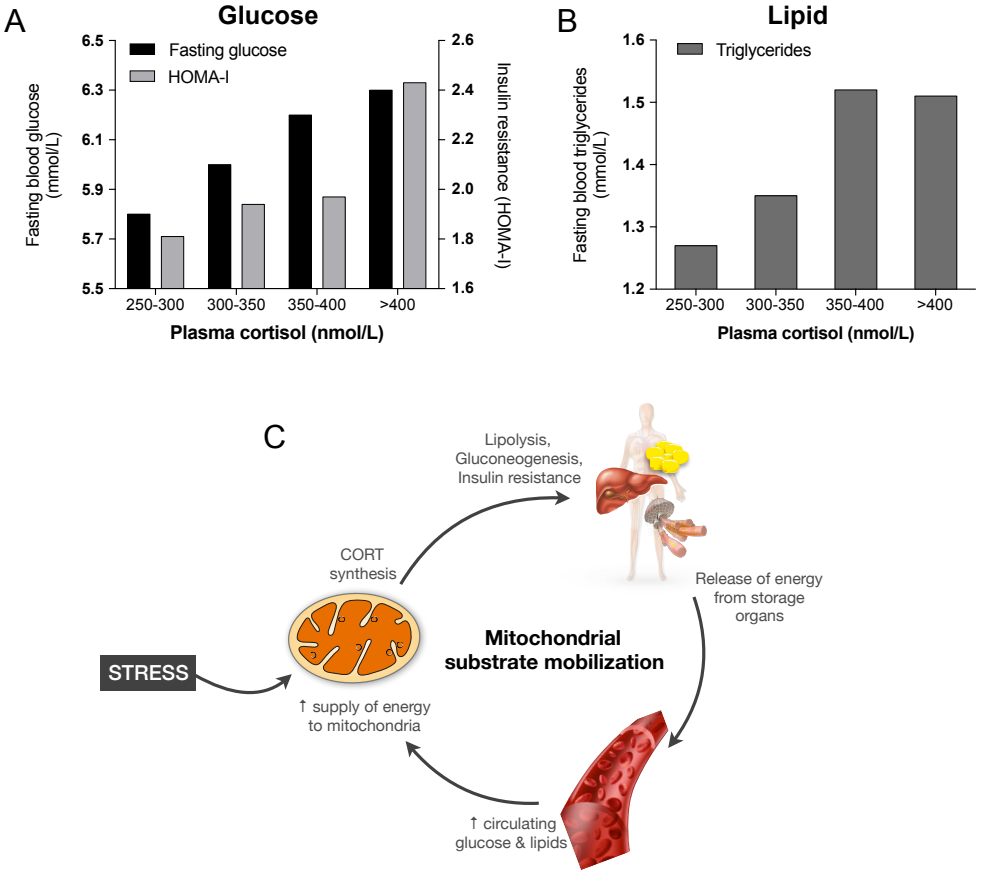

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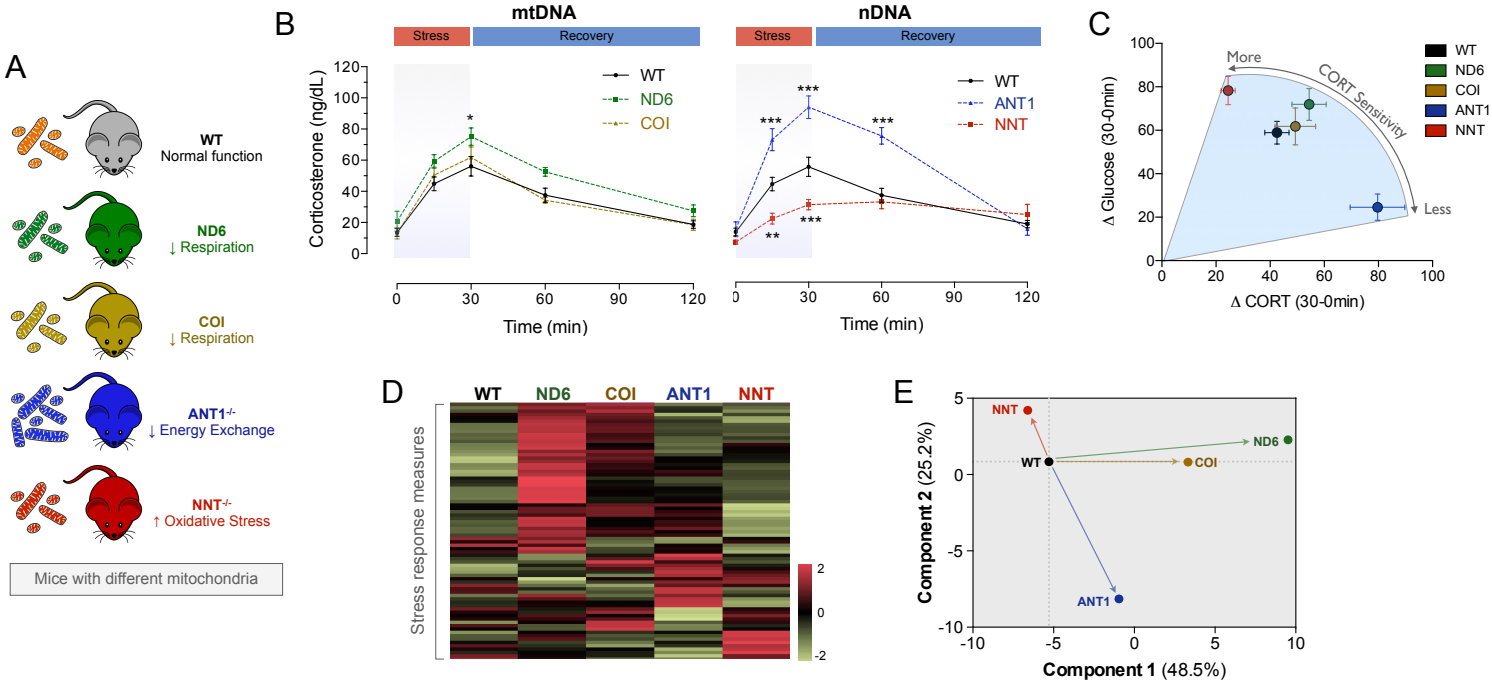

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Highlights

1. The flow of energy is the determining factor between life and death
2. Mitochondria sustain life and allostasis via energy transformation and signaling
3. Molecular, cellular, and behavioral responses to stress increase energy demand
4. Mitochondria produce hormones – mitokines – that influence stress physiology
5. Research is needed to define the role of mitochondria in human stress responses

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Graphical abstract